JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b00197 • Publication Date (Web): 09 Mar 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of Alkylidene(*gem*-Difluorocyclopropanes) from Propargyl Glycolates by a One-Pot Difluorocyclopropenation/Ireland-Claisen Rearrangement Sequence

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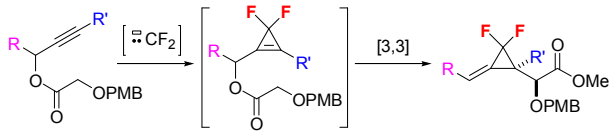
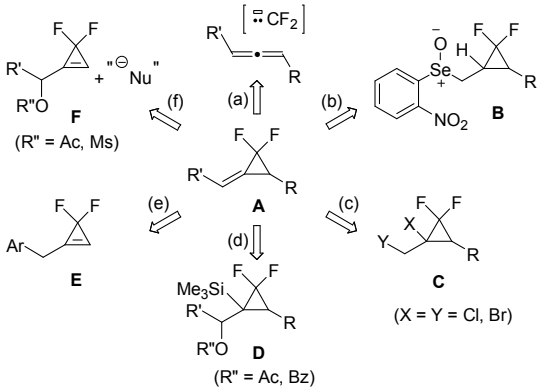


ABSTRACT: A one-pot difluorocyclopropenation/Ireland-Claisen rearrangement sequence applied to readily available propargyl glycolates was developed as a route toward functionalized alkylidene(*gem*-difluorocyclopropanes). This strategy conveniently avoids the isolation of the unstable 3,3-difluorocyclopropenylcarbinyl glycolates arising from the difluorocyclopropenation. The Ireland-Claisen rearrangement proceeds with high diastereoselectivity and chirality transfer to afford alkylidene(*gem*-difluorocyclopropanes) incorporating a quaternary stereocenter and a protected glycolic acid moiety, which are useful building blocks for the preparation of functionalized *gem*-difluorocyclopropanes.

In the development of drug candidates, medicinal chemists have often relied on the beneficial effects of the incorporation of a cyclopropyl ring[1] or fluorine atoms[2] in a molecule for conformational control as well as improvement of the potency, metabolic stability, membrane permeability and pharmacokinetic properties. Accordingly, the development of efficient and stereoselective methods for the preparation of functionalized monofluoro- or difluorocyclopropanes, which combine both of these latter relevant structural features, has elicited significant interest.[3–5] Among the different classes of difluorocyclopropanes, the synthesis and reactivity of alkylidene(*gem*-difluorocyclopropanes) **A** which could serve as valuable precursors of a wide variety of *gem*-difluorocyclopropanes, has not been thoroughly investigated.[3,5] The three-membered ring in compounds **A** can be constructed by regioselective cyclopropanation of the more electron-rich bond of allenes with difluorocarbene, generated from various precursors (Scheme 1, route a).[6] However, further reaction of alkylidene(*gem*-difluorocyclopropanes) **A** with difluorocarbene can occur and this strategy has seldom been applied to functionalized allenes besides examples of difluorocyclopropanation of one β-allenic ester[6e] and γ,γ-dialkylated allenyl sulfones.[6f] Alternatively, the exocyclic alkene in alkylidene(*gem*-difluorocyclopropanes) **A** can be created by an elimination step applied to selenoxydes **B** derived from *gem*-difluorocyclopropanemethanols (Scheme 1, route b),[7,8] vicinal dihalides **C** (Scheme 1, route c)[8,9] or esters derived from (*gem*-difluoro-α-trimethylsilylcyclopropyl)carbinols **D** (Scheme 1, route d).[10] 3,3-Difluorocyclopropenes have occasionally been considered as precursors of alkylidene(*gem*-difluorocyclopropanes) **A**. One example of isomerization of an (arylmethyl)difluorocyclopropene **E**, in the presence of a base (DBU), was disclosed but conjugation of the olefin with the aromatic ring provides the driving force of this transformation (Scheme 1, route e).[11] In contrast to the non-fluorinated series, it is worth noting that methylene(*gem*-difluorocyclopropanes) are isomerized to the thermodynamically

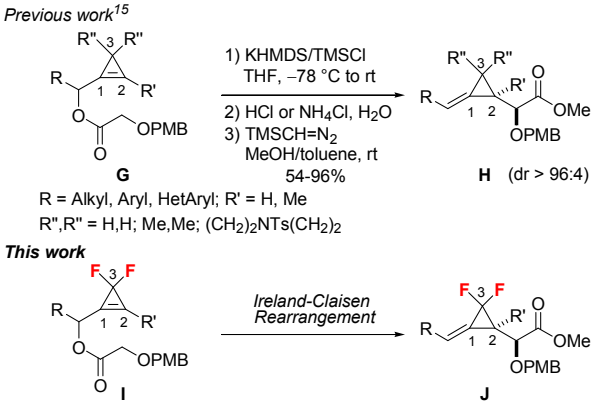
favored 1-methyl(3,3-difluorocyclopropenes) under basic conditions.[10] Whereas the strong electron-withdrawing effect of fluorine provides a partial aromatic cyclopropenium character to *gem*-difluorocyclopropenes,[3,12] this property also paradoxically accounts for their chemical instability and ease of hydrolysis into cyclopropenones.[3,13] Two examples of S_N2' nucleophilic displacements of cyclopropenylcarbinyl esters and mesylates **F** (with K-Selectride® and $Me_2CuLi•LiCN$, respectively) were also reported in the context of the synthesis of pyrethrinoids analogs (Scheme 1, route f).[14]

Scheme 1. Synthetic approaches toward alkylidene(*gem*-difluorocyclopropanes) A



Thus, the development of alternative routes toward alkylidene(*gem*-difluorocyclopropanes) **A** remains a challenging goal and in particular processes that would allow a stereoselective access to functionalized and highly substituted compounds. Recently, we reported that cyclopropenylcarbinyl glycolates **G** undergo an efficient and highly diastereoselective Ireland-Claisen rearrangement leading to functionalized alkylidenecyclopropanes **H** incorporating a glycolic acid moiety.[15,16] Herein, we disclose our results on the expansion of the scope of the Ireland-Claisen rearrangement of cyclopropenylcarbinol derivatives to 3,3-difluorocyclopropenylcarbinyl glycolates **I** with the aim of synthesizing functionalized alkylidene(*gem*-difluorocyclopropanes) **J** (Scheme 2). One critical issue was whether the unstable 3,3-difluorocyclopropenes **I**[13] could withstand the conditions of the Ireland-Claisen rearrangement and how the fluorine atoms would affect the reactivity.

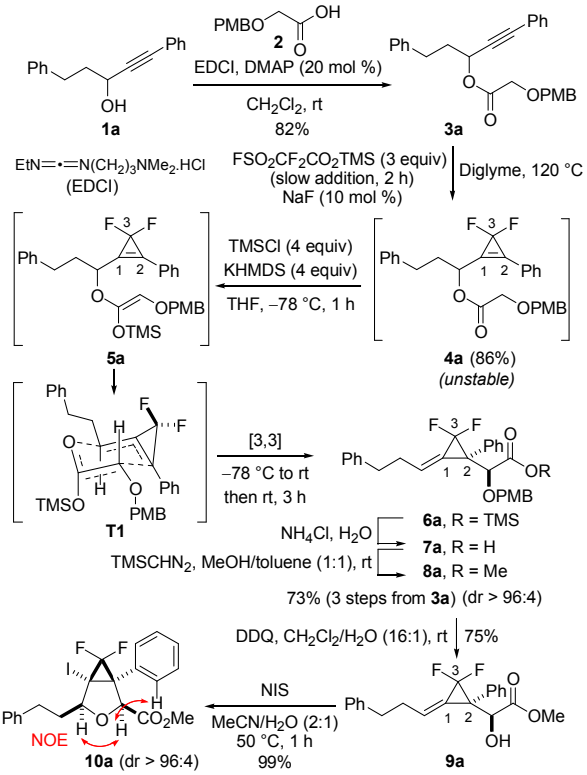
Scheme 2. Ireland-Claisen Rearrangement of Cyclopropenylcarbinyl Glycolates



Our initial studies were conducted with propargyl glycolate **3a**, readily prepared by condensation of alcohol **1a** with carboxylic acid **2** in the presence of EDCI and DMAP (20 mol %) (CH_2Cl_2, rt, 82% yield). The difluorocyclopropenation of the triple bond in **3a** was initially attempted using Ruppert-Prakash's reagent ($TMSCF_3$, 2 equiv) in the presence of NaI (2.2 equiv) in THF (sealed tube, 80 °C, 2 h)[17] but the 3,3-difluorocyclopropene **4a** was isolated in modest yield (43%) because unidentified side-products were formed. Much more satisfactory results were obtained by slow addition (*via* syringe pump within 2 h) of an excess of Dolbier's reagent (trimethylsilyl fluorosulfonyldifluoroacetate, TFDA)[18] to a concentrated solution (c = 2 M) of propargyl glycolate **3a** in diglyme at 120 °C. The desired 3,3-difluorocyclopropene **4a** was isolated in 86% yield after purification by flash column chromatography on silica gel. However, as already mentioned for other 3,3-difluorocyclopropenes,[13] compound **4a** turned out to be unstable and underwent rapid decomposition into a complex mixture of products, despite the presence of a phenyl substituent on the double bond. To overcome the instability of 3,3-difluorocyclopropenylcarbinyl glycolates, we reasoned that isolation of compound **4a** may not be required[19] because gaseous (CO_2, SO_2) or volatile (TMSF) by-products are generated

during the difluorocyclopropenation with TFDA and the ethereal solvent (diglyme) should be compatible with the conditions of the Ireland-Claisen rearrangement. Thus, once the difluorocyclopropenation of alkyne **3a** was complete, the reaction mixture was diluted with THF and the residual gaseous/volatile by-products were removed by sparging with argon. Enolization of the 3,3-difluorocyclopropenylcarbinyl glycolate **4a** was then triggered by successive addition of TMSCl (4 equiv) and KHMDS (4 equiv) at –78 °C, to generate the corresponding silylketene acetal **5a** of (*Z*) configuration.[15,20] Upon warming to rt, **5a** underwent a [3,3]-sigmatropic rearrangement leading to trimethylsilyl ester **6a**. After hydrolysis under slightly acidic conditions, the resulting crude carboxylic acid **7a** was treated with trimethylsilyldiazomethane[21] to afford methyl ester **8a**, as a single detectable diastereomer by ^{1}H NMR spectroscopy (dr > 96:4). After purification by flash column chromatography on silica gel, alkylidene(*gem*-difluoro-cyclopropane) **8a** was isolated in a satisfying 73% overall yield (three steps from glycolate **3a**). The synthesis of **8a** could be easily achieved at the gram scale (1.1 g) with no adverse effect on the overall yield (72%). Cleavage of the PMB ether in compound **8a** with DDQ afforded the secondary alcohol **9a** (75%) which was subjected to an intramolecular iodoetherification[22] that led to oxabicyclic compound **10a** as a single detectable diastereomer (dr > 96:4) in quantitative yield. The *cis* relationship between the protons adjacent to the oxygen atom and the phenyl group at the ring junction in **10a**, which was assigned by NMR spectroscopy (NOESY), confirmed the relative configuration of two adjacent stereocenters as well as the (Z) configuration of the exocyclic alkene in alkylidene(*gem*-difluorocyclopropane) **8a**. As observed with other cyclopropenylcarbinyl glycolates,[15] the Ireland-Claisen rearrangement of **4a** proceeds through a chairlike transition state **T1** in which the 2-phenylethyl group preferentially occupies an equatorial position (Scheme 3).[15,20]

Scheme 3. One-pot difluorocyclopropenation of propargyl glycolate 3a and Ireland-Claisen rearrangement of 3,3-difluorocyclopropenylmethyl glycolate 4a



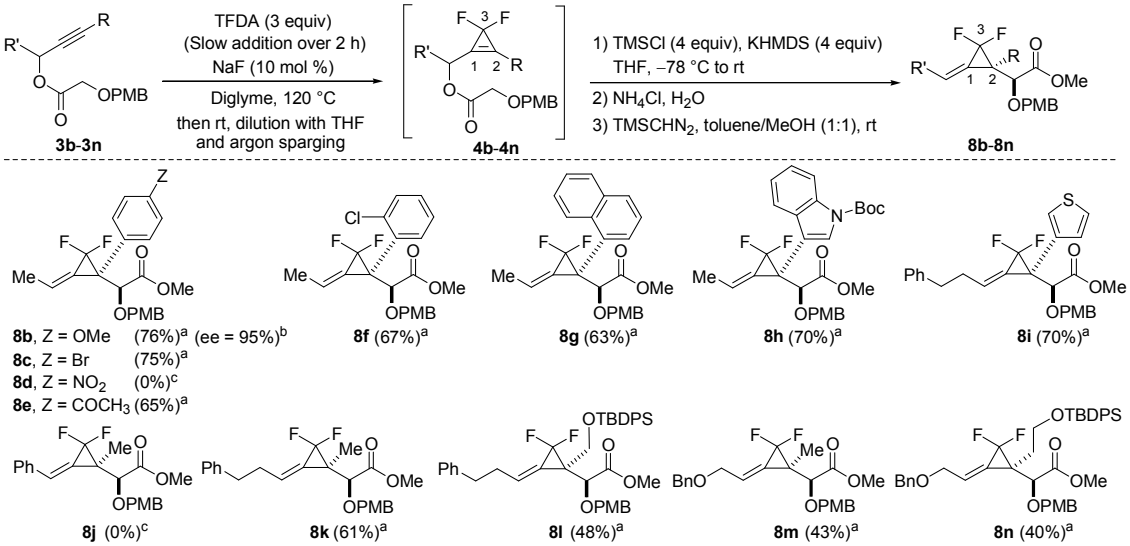
The use of propargyl alcohols as precursors of 3,3-difluorocyclopropenylcarbinyl glycolates was an appealing feature of the method because these latter alcohols are readily accessible and possibly in an enantioenriched form.[23] To determine the substrate scope of the one-pot difluorocyclopropenation/Ireland-Claisen rearrangement sequence, the reactivity of diversely substituted propargyl glycolates **3b-3n** was investigated (Scheme 4). The behaviour of glycolates **3b-3g** possessing an aromatic group at the acetylenic position was first explored. The one-pot difluorocyclopropenation/Ireland-Claisen rearrangement sequence was successfully implemented for **3b**, incorporating a *p*-methoxyphenyl substituent, as shown by the isolation of ethylidene(*gem*-difluoro-cyclopropane) **8b** (76%, three steps from **3b**). Importantly, when enantioenriched (*S*)-**3b** (ee = 96%) was used as substrate, the corresponding optically active ethylidene-(*gem*-difluorocyclopropane) **8b** was obtained (72%,

ee = 95%), thereby indicating that chirality transfer occurred in the Ireland-Claisen rearrangement of enantioenriched glycolate **4b**.[24] The sequence also operated well in the case of **3c** possessing a *p*-bromophenyl substituent and produced alkylidene(*gem*-difluorocyclopropane) **8c** (75%, three steps from **3c**). However, one limitation was identified with glycolate **3d** substituted by *p*-nitrophenyl group. Although the difluorocyclopropenation of **3d** proceeded efficiently, the Ireland-Claisen rearrangement of the resulting 3,3-difluorocyclopropenylcarbinyl glycolate **4d** could not be achieved and led to a complex mixture of products. This result was explained by considering that the *p*-nitrophenyl group would significantly increase the acidity of the proton on the carbon adjacent to the difluorocyclopropene (at the α position of the oxygen atom). Competitive abstraction of this proton by the base would generate a carbanion adjacent to the difluorocyclopropene ring that may be responsible for the observed degradation of **4d**. Although ethylidene(*gem*-difluorocyclopropane) **8e** was obtained in good yield (65%) from glycolate **3e** possessing an electron-withdrawing acetyl group at the *para* position of the aromatic ring, the methyl ketone was presumably converted into a silyl enol ether under the conditions of the Ireland-Claisen rearrangement. The presence of an aromatic group substituted at the *ortho* position did not hamper the efficiency of the sigmatropic rearrangement as shown with the successful formation of ethylidene(*gem*-difluorocyclopropanes) **8f** (67%) and **8g** (63%), possessing a 2-chlorophenyl and a 1-naphthyl substituent at the quaternary stereocenter, respectively. Interestingly, the presence of atropodiastereomers was observed in the NMR spectra of compounds **8f** and **8g**, because of restricted rotation around the aryl–C2 bond. Propargyl glycolates possessing a moderately electron-rich heteroaromatic group at the acetylenic position were compatible with the difluorocyclopropenation/Ireland-Claisen rearrangement sequence. Hence, the preparation of the alkylidene(*gem*-difluorocyclopropanes) **8h** and **8i**,

possessing a *N*-Boc-indol-3-yl and a 3-thienyl group, respectively, was achieved in good overall yield (70%) (Scheme 4).

Further exploration of the substrate scope was carried out with propargyl glycolates bearing an alkyl chain at the acetylenic position.[25] For such substrates, the substituent at the propargylic position could not be a phenyl group. Indeed, whereas the difluorocyclopropenation of glycolate **3j** could be achieved, the resulting difluorocyclopropene **4j** decomposed under the conditions of the Ireland-Claisen rearrangement. This behaviour is in striking contrast with the reactivity of the related 3,3-dimethylcyclopropenylcarbinyl glycolates **G** in the Ireland-Claisen rearrangement which accommodate an aromatic ring at the adjacent position (Scheme 2).[15] The strong electron-withdrawing effect of the fluorine atoms on the cyclopropene probably enhances the acidity of the proton on the adjacent (benzylic) carbon. As previously observed with cyclopropene **4d**, competitive abstraction of this latter proton by the base would account for the failure to achieve the Ireland-Claisen rearrangement of **4j**. Accordingly, the reactivity of glycolates **3k-3n**, substituted at the propargylic position by aliphatic substituents (a 2-phenylethyl or a benzyloxymethyl group), was examined. The corresponding alkylidene(*gem*-difluoro-cyclopropanes) **8k** (61%), **8l** (48%), **8m** (43%) and **8n** (40%) were isolated in good to moderate overall yields. Interestingly, protected hydroxymethyl and 2-hydroxyethyl substituents could be introduced on the quaternary stereocenter (C2) in *gem*-difluorocyclopropanes **8l** and **8n**. The lower yields generally observed for alkylidene(*gem*-difluorocyclopropanes) **8k-8n**, compared to those attained with **8b**, **8c**, **8e-8i** possessing an aromatic group, is due to the lower stability of the alkyl-substituted *gem*-difluorocyclopropenes (Scheme 4).[13]

Scheme 4. Scope of propargyl glycolates

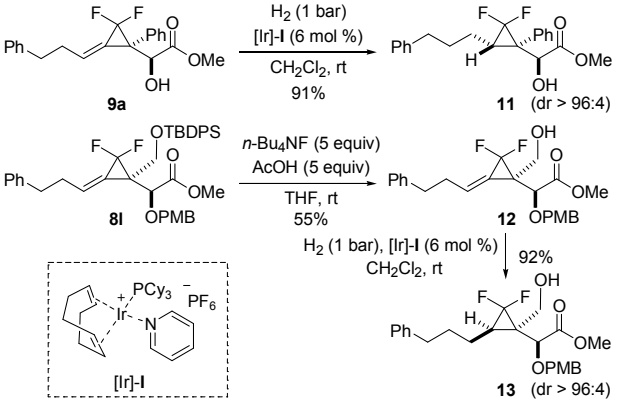


[a] Isolated yield of analytically pure material (three steps from the corresponding propargyl glycolates). [b] Obtained from optically active (*S*)-**3b** (ee = 96%). [c] The corresponding *gem*-difluorocyclopropenes were formed but decomposed under the conditions of the Ireland-Claisen rearrangement.

To illustrate that alkylidene(*gem*-difluorocyclopropanes) **J** enable access to other classes of substituted *gem*-difluorocyclopropanes, a few transformations of these latter compounds were carried out. To our knowledge, no examples of hydrogenation of alkylidene(*gem*-difluoro-cyclopropanes) have been disclosed to date, so the feasilibity of this transformation which would create an additional stereocenter was worth studying. Because the presence of a quaternary stereocenter at C2 in the alkylidenecyclopropanes **J** would not allow for a satisfactory discrimination of the diastereofaces of the exocyclic alkene,[16b] a substrate-directed hydrogenation was investigated.[15] Thus, the α-hydroxy ester **9a**, obtained from **8a** by cleavage of the PMB ether, underwent a highly diastereoselective hydrogenation in the presence of Crabtree's catalyst [Ir]-**I** (6 mol %)[26] which afforded *gem*-difluorocyclopropane **11** in 91% yield with high diastereoselectivity (dr > 96:4). It is worth noting that no ring-opening occurred under these conditions. In the case of compound **8l**, cleavage of the silyl

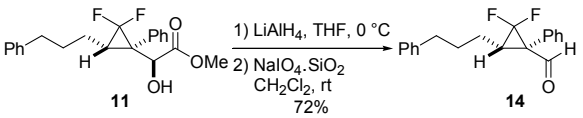
ether afforded the primary alcohol **12** (55%) which underwent a highly diastereoselective directed hydrogenation leading to *gem*-difluorocyclopropane **13** (92%) (Scheme 5).[27]

Scheme 5. Diastereoselective hydrogenation of alkylidene-(*gem*-difluorocyclopropanes)



The glycolic acid moiety can be converted into a valuable aldehyde functional group. Thus, reduction of the methyl ester **11** with $LiAlH_4$, followed by oxidative cleavage of the resulting 1,2-diol with $NaIO_4$ adsorbed on silica gel,[28] delivered aldehyde **14** (72%, two steps from **11**) possessing an adjacent quaternary stereocenter on the difluorinated cyclopropane (Scheme 6).[29]

Scheme 6. Synthesis of aldehyde 14



In conclusion, we have developed a one-pot sequence involving the difluorocyclopropenation of propargyl glycolates followed by the Ireland-Claisen rearrangement of the resulting 3,3-difluorocyclopropenyl glycolates as a route toward of alkylidene(*gem*-difluoro-cyclopropanes) incorporating a quaternary stereocenter and a glycolic acid moiety. The substrates are readily available from propargylic alcohols and the Ireland-Claisen

rearrangement of 3,3-difluorocyclopropenylcarbinyl glycolates proceeds with high diastereoselectivity and chirality transfer. This sequence provides an interesting entry to a variety of *gem*-difluorocyclopropanes that would not be readily obtained by other routes.

EXPERIMENTAL SECTION

General information. All reactions were carried out under anhydrous conditions, using flame-dried glassware and under an argon atmosphere. THF was distilled from Na/benzophenone. CH_2Cl_2, Et_3N, *i*Pr_2NEt and diglyme were distilled from CaH_2. Other reagents were obtained from commercial suppliers and used as received. Flash chromatography was performed on silica gel (230-400 mesh). Optical rotations were measured using a polarimeter with a 1 dm path length at 589 nm. IR spectra were recorded with attenuated total reflectance (ATR) sampling technique. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded at 400 MHz, 100 MHz and 282 MHz, respectively. The chemical shifts (δ) are reported in parts per million (ppm) and were referenced to the residual isotopomer solvent signals ($CHCl_3$: δ = 7.26 ppm, C_6D_5H: δ = 7.16 ppm, $CD_3S(=O)CHD_2$: δ = 2.50 ppm) for ^{1}H NMR spectra, the solvent signal ($CDCl_3$: δ = 77.16 ppm, C_6D_6: δ = 128.06 ppm, DMSO-d_6: δ = 39.52 ppm) for ^{13}C NMR spectra or to external $CFCl_3$ (δ = 0 ppm) for ^{19}F spectra. Coupling constants are given in Hertz (Hz) and multiplicities are indicated using the conventional abbreviations (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or overlap of non-equivalent resonances, br = board, app = apparent). All ^{13}C spectra were broadband ^{1}H-decoupled and the carbon environment (C, CH, CH_2 or CH_3) was deduced from DEPT experiments. High resolution mass spectra (HRMS) were performed with an orbitrap mass analyzer by electrospray ionization. Enantiomeric purities of optically active compounds were determined by supercritical fluid chromatography (SFC) analysis, after calibration with the racemic sample, using a mixture of supercritical CO_2 ($scCO_2$) and

MeOH as eluent and a chiral stationary phase. The known propargylic alcohols **1a**,[30] **1j**,[31] **1k**,[32] **1m**[33] and **1n**[34] were prepared by reaction of the corresponding lithium alkynylide to the appropriate aldehyde. Alcohol **1i** was prepared in the same manner but was directly converted into glycolate **3i**. The known propargylic alcohols **1b**,[35] **1c**,[36] **1d**,[37] **1e**,[38] **1g**,[39] were prepared by Sonogashira cross-coupling reactions between the corresponding (hetero)aromatic iodide and propargyl alcohol possessing a terminal alkyne. Enantioenriched (*S*)-**1b** was prepared in a similar manner as racemic **1b**, by Sonogashira cross-coupling between commercially available (*S*)-3-butyn-2-ol and 4-iodoanisole.[35]

*(S)-4-(4-Methoxyphenyl)but-3-yn-2-ol ((S)-**1b**).* To a degassed mixture (argon sparging, 10 min) of $Pd(PPh_3)_2Cl_2$ (25.6 mg, 0.036 mmol, 2 mol %), CuI (17.4 mg, 0.091 mmol, 5 mol %) and 4-iodoanisole (426 mg, 1.82 mmol) in THF (7 mL) at 0 °C, were added successively (*S*)-3-butyn-2-ol (214 μL, 2.73 mmol, 1.5 equiv) and Et_3N (760 μL, 13.7 mmol, 3 equiv). After 16 h stirring at rt, the reaction mixture was filtered through Celite (EtOAc). The filtrate was successively washed with a saturated aqueous solution of NH_4Cl, brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/EtOAc = 80:20) to afford 279 mg (87%) of (*S*)-**1b** as a yellow oil; IR: ν 3357, 2228, 1607, 1509, 1290, 1248, 1174, 1104, 1029, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (app d, J = 8.9 Hz, 2H), 6.82 (app d, J = 8.9 Hz, 2H), 4.74 (m, 1H), 3.80 (s, 3H), 2.11 (d, J = 5.2 Hz, 1H, OH), 1.54 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7 (C), 133.2 (2CH), 114.8 (C), 114.0 (2CH), 89.7 (C), 84.0 (C), 59.0 (CH), 55.4 (CH_3), 24.6 (CH_3). Spectral data matched those previously reported for this compound.[35] $[\alpha]_D^{20}$ –21.4 (*c* 0.252, $CHCl_3$) {$[\alpha]_{D\,litt}^{26}$ –29.6 (*c* 1.44, $CHCl_3$)}.[40] The enantiomeric excess of (*S*)-**1b** was determined by supercritical fluid chromatography using a chiral stationary phase (AD-H column, 100 bar, 3 mL/min, $scCO_2$/MeOH = 96:4): minor (*R*)-enantiomer: t_R = 10.9 min; major (*S*)-enantiomer: t_R = 11.9 min. ee = 96%.

*4-(2-Chlorophenyl)but-3-yn-2-ol (**1f**).* Prepared by Sonogashira cross-coupling between 1-chloro-2-iodobenzene and 3-butyn-2-ol. After purification by flash chromatography (petroleum ether/EtOAc = 80:20), **1f** was isolated as an orange oil (958 mg, 97%); IR: ν 3320, 1473, 1105, 1061, 1031, 935, 855, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (dd, J = 7.6, 1.8 Hz, 1H), 7.35 (dd, J = 7.8, 1.6 Hz, 1H), 7.20 (app td, J = 7.7, 1.9 Hz, 1H), 7.15 (app td, J = 7.5, 1.5 Hz, 1H), 4.81 (q, J = 6.6 Hz, 1H), 2.94 (s, 1H, OH), 1.57 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9 (C), 133.4 (CH), 129.4 (CH), 129.2 (CH), 126.4 (CH), 122.6 (C), 96.4 (C), 80.7 (C), 58.8 (CH), 24.3 (CH_3); HRMS (ESI) *m/z* calcd for $C_{10}H_9ClONa$ [M (^{35}Cl) + Na]$^+$ and [M (^{37}Cl) + Na]$^+$: 203.0234 and 205.0205, found: 203.0237 and 205.0206.

*4-(Naphthalen-1-yl)but-3-yn-2-ol (**1g**).* Prepared by Sonogashira cross-coupling between 1-iodonaphthalene and 3-butyn-2-ol. After purification by flash chromatography (petroleum ether/EtOAc = 80:20), **1g** was isolated as a yellow oil (1.06 g, 99%); IR: ν 3316, 3058, 2221, 1587, 1507, 1395, 1327, 1118, 1079, 799, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (br d, J = 8.2 Hz, 1H), 7.86–7.81 (m, 2H), 7.67 (dd, J = 7.1, 1.1 Hz, 1H), 7.61–7.49 (m, 2H), 7.41 (m, 1H), 4.93 (m, 1H), 2.43 (br s, 1H, OH), 1.68 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.3 (C), 133.2 (C), 130.6 (CH), 129.0 (CH), 128.4 (CH), 126.9 (CH), 126.5 (CH), 126.1 (CH), 125.2 (CH), 120.3 (C), 96.1 (C), 82.2 (C), 59.2 (CH), 24.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{14}H_{12}ONa$ [M + Na]$^+$: 219.0780, found: 219.0782.

*tert-Butyl 3-(3-hydroxybut-1-yn-1-yl)-1H-indole-1-carboxylate (**1h**).* Prepared by Sonogashira cross-coupling between *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate[41] and 3-butyn-2-ol. After purification by flash chromatography (petroleum ether/EtOAc = 80:20), **1h** was isolated as an

orange solid (1.26 g, 97%); Mp 104–106 °C; IR: ν 3376, 2230, 1738, 1452, 1369, 1232, 1155, 1088, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.1 Hz, 1H), 7.74 (s, 1H), 7.64 (app br d, J = 7.8 Hz, 1H), 7.38–7.24 (m, 2H), 4.83 (m, 1H), 2.16 (d, J = 5.3 Hz, 1H, OH), 1.66 (s, 9H), 1.60 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2 (C), 134.7 (C), 130.5 (C), 129.1 (CH), 125.3 (CH), 123.3 (CH), 120.1 (CH), 115.3 (CH), 102.8 (C), 94.7 (C), 84.5 (C), 76.1 (C), 59.1 (CH), 28.2 ($3CH_3$), 24.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{17}H_{19}NO_3Na$ $[M + Na]^+$: 308.1257, found: 308.1259.

*6-[(tert-Butyldiphenylsilyl)oxy]-1-phenylhex-4-yn-3-ol (**1l**).* To a solution of *tert*-butyl-diphenyl(2-propynyloxy)silane[42] (1.20 g, 4.06 mmol, 1.5 equiv) in THF (14 mL) at –78 °C, was added dropwise a solution of *n*-BuLi (1.52 mL, 2.5 M in hexanes, 3.79 mmol, 1.4 equiv). After 0.5 h stirring at –78 °C, 3-phenylpropanal (400 µL, 2.71 mmol) was added dropwise. The reaction mixture was allowed to warm to rt, stirred for 0.5 h and then poured into a saturated aqueous solution of NH_4Cl. The resulting mixture was extracted with Et_2O and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (petroleum ether/Et_2O = 90:10 to 70:30) to afford 1.10 g (94%) of **1l** as a colorless oil; IR: ν 3370, 1428, 1372, 1260, 1129, 1111, 1070, 1029, 998; 823, 739, 698, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.70 (m, 4H), 7.46–7.35 (m, 6H), 7.31–7.25 (m, 2H), 7.22–7.14 (m, 3H), 4.39 (d, J = 1.6 Hz, 2H), 4.28 (m, 1H), 2.72 (t, J = 7.8 Hz, 2H), 1.97–1.86 (m, 2H), 1.61 (d, J = 5.2 Hz, 1H, OH), 1.06 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4 (C), 135.7 (4CH), 133.2 (2C), 129.9 (2CH), 128.5 (2CH), 128.4 (2CH), 127.7 (4CH), 126.0 (CH), 86.0 (C), 83.7 (C), 61.7 (CH), 52.7 (CH_2), 39.0 (CH_2), 31.3 (CH_2), 26.7 (3 CH_3), 19.2 (C); HRMS (ESI) *m/z* calcd for $C_{28}H_{32}O_2SiNa$ $[M + Na]^+$: 451.2064, found: 451.2054.

Representative procedure for the preparation of propargyl glycolates: To a solution of propargyl alcohol **1a** (1.06 g, 4.48 mmol, 1.0 equiv) and (4-methoxybenzyloxy)acetic acid **2**[43] (1.32 g, 6.72 mmol, 1.5 equiv) in CH_2Cl_2 (20 mL) at 0 °C, were added EDCI (1.29 g, 6.72 mmol, 1.5 equiv) and DMAP (109 mg, 0.896 mmol, 20 mol %). After stirring overnight at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 80:20) to afford 1.33 g (72%) of glycolate **3a** as a colorless oil.

*1,5-Diphenylpent-1-yn-3-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3a**).* IR: ν 2231, 1757, 1612, 1513, 1248, 1118, 1033, 821, 757, 692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.44 (m, 2H), 7.36–7.28 (m, 7H), 7.24–7.20 (m, 3H), 6.89 (app d, J = 8.7 Hz, 2H), 5.72 (t, J = 6.5 Hz, 1H), 4.60 (s, 2H), 4.14 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.07 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 2.85 (t, J = 7.9 Hz, 2H), 2.27–2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 159.6 (C), 140.7 (C), 132.0 (2CH), 130.0 (2CH), 129.2 (C), 128.9 (CH), 128.7 (2CH), 128.5 (2CH), 128.4 (2CH), 126.3 (CH), 122.2 (C), 114.0 (2CH), 86.3 (C), 85.8 (C), 73.1 (CH_2), 66.9 (CH_2), 64.7 (CH), 55.4 (CH_3), 36.5 (CH_2), 31.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{27}H_{26}O_4Na$ $[M + Na]^+$: 437.1723, found: 437.1722.

*4-(4-Methoxyphenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3b**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3b** was isolated as a yellow oil (788 mg, 98%); IR: ν 2229, 1754, 1607, 1510, 1291, 1246, 1174, 1106, 1083, 1025, 946, 831, 796, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (app d, J = 8.9 Hz, 2H), 7.31 (app d, J = 8.8 Hz, 2H), 6.88 (app d, J = 8.7 Hz, 2H), 6.82 (app d, J =

8.9 Hz, 2H), 5.78 (q, J = 6.7 Hz, 1H), 4.58 (s, 2H), 4.13 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.08 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.793 (s, 3H), 3.792 (s, 3H), 1.60 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 160.0 (C), 159.6 (C), 133.5 (2CH), 130.0 (2CH), 129.2 (C), 114.3 (C), 114.01 (2CH), 114.00 (2CH), 85.7 (C), 85.1 (C), 73.1 (CH_2), 67.0 (CH_2), 61.7 (CH), 55.4 ($2CH_3$), 21.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{21}H_{22}O_5Na$ $[M + Na]^+$: 377.1359, found: 377.1361.

*(S)-4-(4-Methoxyphenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate ((S)-**3b**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), (*S*)-**3b** was isolated as a yellow oil (389 mg, 92%); $[\alpha]_D^{20}$ –56.5 (*c* 0.154, $CHCl_3$) (ee = 96%).

*4-(4-Bromophenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3c**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3c** was isolated as a white solid (443 mg, 82%); Mp 72–74 °C; IR: ν 1756, 1613, 1586, 1513, 1248, 1188, 1109, 1070, 1030, 1011, 823 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (app d, J = 8.7 Hz, 2H), 7.33–7.27 (m, 4H), 6.88 (app d, J = 8.7 Hz, 2H), 5.75 (q, J = 6.7 Hz, 1H), 4.59 (s, 2H), 4.13 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.08 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 1.60 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 159.7 (C), 133.4 (2CH), 131.7 (2CH), 130.0 (2CH), 129.1 (C), 123.2 (C), 121.2 (C), 114.0 (2CH), 88.2 (C), 84.1 (C), 73.2 (CH_2), 66.9 (CH_2), 61.4 (CH), 55.4 (CH_3), 21.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{19}BrO_4Na$ $[M\,(^{79}Br) + Na]^+$ and $[M\,(^{81}Br) + Na]^+$: 425.0359 and 427.0338, found: 425.0360 and 427.0337.

*4-(4-Nitrophenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3d**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **3d** was isolated as a yellow oil (770 mg, 99%); IR: ν 1756, 1612, 1595, 1514, 1342, 1247, 1186, 1107, 1084,

1028, 855, 750, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (app d, J = 9.0 Hz, 2H), 7.54 (app d, J = 9.0 Hz, 2H), 7.28 (app d, J = 8.8 Hz, 2H), 6.85 (app d, J = 8.8 Hz, 2H), 5.76 (q, J = 6.7 Hz, 1H), 4.57 (s, 2H), 4.13 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.09 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.76 (s, 3H), 1.61 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3 (C), 159.5 (C), 147.3 (C), 132.6 (2CH), 129.8 (2CH), 128.95 (C), 128.88 (C), 123.5 (2CH), 113.8 (2CH), 92.1 (C), 83.0 (C), 73.0 (CH_2), 66.7 (CH_2), 60.9 (CH), 55.2 (CH_3), 21.1 (CH_3); HRMS (ESI): calcd for $C_{20}H_{19}NO_6Na$ $[M + Na]^+$: 392.1105, found: 392.1103.

*4-(4-Acetylphenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3e**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3e** was isolated as a yellow solid (788 mg, 98%); Mp 76–78 °C; IR: ν 1756, 1683, 1602, 1514, 1249, 1182, 1108, 1086, 1029, 955, 833 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (app d, J = 8.6 Hz, 2H), 7.51 (app d, J = 8.6 Hz, 2H), 7.31 (app d, J = 8.7 Hz, 2H), 6.88 (app d, J = 8.7 Hz, 2H), 5.78 (q, J = 6.7 Hz, 1H), 4.59 (s, 2H), 4.14 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.09 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 2.60 (s, 3H), 1.62 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.4 (C), 169.5 (C), 159.6 (C), 136.7 (C), 132.1 (2CH), 130.0 (2CH), 129.1 (C), 128.3 (2CH), 127.0 (C), 114.0 (2CH), 90.2 (C), 84.3 (C), 73.1 (CH_2), 66.9 (CH_2), 61.3 (CH), 55.4 (CH_3), 26.7 (CH_3), 21.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{22}O_5Na$ $[M + Na]^+$: 389.1359, found: 389.1361.

*4-(2-Chlorophenyl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3f**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3f** was isolated as an orange oil (572 mg, 96%); IR: ν 1756, 1612, 1513, 1247, 1187, 1107, 1087, 1060, 1026, 948, 820, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 7.4, 2.0 Hz, 1H), 7.38 (dd, J = 7.9, 1.5 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.25 (app td, J = 7.5, 1.8 Hz, 1H),

7.19 (app td, J = 7.6, 1.4 Hz, 1H), 6.88 (app d, J = 8.8 Hz, 2H), 5.82 (q, J = 6.7 Hz, 1H), 4.59 (s, 2H), 4.14 (d_{ABsyst}, J = 16.5 Hz, 1H,), 4.09 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.79 (s, 3H), 1.64 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 159.6 (C), 136.2 (C), 133.6 (CH), 130.0 (2CH), 129.8 (CH), 129.3 (CH), 129.1 (C), 126.5 (CH), 122.1 (C), 114.0 (2CH), 92.2 (C), 81.8 (C), 73.1 (CH_2), 66.9 (CH_2), 61.4 (CH), 55.3 (CH_3), 21.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{19}ClO_4Na$ [M(^{35}Cl) + Na]$^+$ and [M(^{37}Cl) + Na]$^+$: 381.0864 and 383.0835, found: 381.0864 and 383.0834.

*4-(Naphthalen-1-yl)but-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3g**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3g** was isolated a yellow oil (558 mg, 97%); IR: ν 2225, 1755, 1612, 1586, 1513, 1247, 1191, 1175, 1117, 1073, 1046, 1034, 801, 774 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (app d, J = 8.3 Hz, 1H), 7.84 (app d, J = 7.5 Hz, 2H), 7.69 (dd, J = 7.2, 1.1 Hz, 1H), 7.57 (app ddd, J = 8.3, 6.9, 1.4 Hz, 1H), 7.52 (app ddd, J = 8.1, 6.9, 1.4 Hz, 1H), 7.42 (dd, J = 8.3, 7.2 Hz, 1H), 7.32 (app d, J = 8.7 Hz, 2H), 6.88 (app d, J = 8.7 Hz, 2H), 5.94 (q, J = 6.7 Hz, 1H), 4.62 (s, 2H), 4.18 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.13 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.79 (s, 3H), 1.73 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 159.6 (C), 133.4 (C), 133.2 (C), 131.0 (CH), 130.0 (2CH), 129.4 (CH), 129.2 (C), 128.4 (CH), 127.1 (CH), 126.6 (CH), 126.1 (CH), 125.2 (CH), 119.8 (C), 114.0 (2CH), 91.9 (C), 83.3 (C), 73.1 (CH_2), 67.0 (CH_2), 61.7 (CH), 55.4 (CH_3), 21.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{24}H_{22}O_4Na$ [M + Na]$^+$: 397.1410, found: 397.1411.

*tert-Butyl 3-[3-({2-[(4-methoxyphenyl)methoxy]acetyl}oxy)but-1-yn-1-yl]-1H-indole-1-carboxylate (**3h**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3h** was isolated as an orange oil (567 mg, 93%); IR: ν 2237, 1739, 1613,

1514, 1453, 1371, 1251, 1233, 1155, 1077, 1034, 821, 760, 749 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (br d, J = 8.1 Hz, 1H), 7.80 (s, 1H), 7.67 (br d, J = 7.7 Hz, 1H), 7.41–7.27 (m, 4H), 6.89 (d, J = 8.7 Hz, 2H), 5.87 (q, J = 6.7 Hz, 1H), 4.62 (s, 2H), 4.17 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.13 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 1.68 (s, 9H), 1.68 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (C), 159.6 (C), 149.0 (C), 134.7 (C), 130.4 (C), 130.0 (2CH), 129.7 (CH), 129.2 (C), 125.3 (CH), 123.4 (CH), 120.1 (CH), 115.3 (CH), 114.0 (2CH), 102.3 (C), 90.6 (C), 84.5 (C), 77.3 (C), 73.1 (CH_2), 66.9 (CH_2), 61.7 (CH), 55.3 (CH_3), 28.2 ($3CH_3$), 21.7 (CH_3); HRMS (ESI) *m/z* calcd for $C_{27}H_{29}NO_6Na$ $[M + Na]^+$: 486.1887, found: 486.1887.

5-Phenyl-1-(thiophen-3-yl)pent-1-yn-3-yl 2-[(4-methoxyphenyl)methoxy]acetate ***(3i)***. To a solution of 3-ethynylthiophene (209 mg, 1.86 mmol, 1.5 equiv) in THF (4 mL) at –78 °C, was added dropwise *n*-BuLi (0.69 mL, 2.5 M solution in hexanes, 1.73 mmol, 1.4 equiv). After 0.5 h stirring at –78 °C, 3-phenylpropanal (183 µL, 1.24 mmol, 1 equiv) was added dropwise. The reaction mixture was warmed to rt, stirred for a further 0.5 h and then poured into a saturated aqueous solution of NH_4Cl. After dilution with ether, the layers were separated and the aqueous phase was extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude propargyl alcohol **1i** was dissolved in CH_2Cl_2 (7 mL) and to the resulting solution were successively added carboxylic acid **2** (364 mg, 1.86 mmol), EDCI (356 mg, 1.86 mmol) and DMAP (30.3 mg, 0.248 mmol). After stirring overnight at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl and diluted with EtOAc. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a saturated aqueous solution of $NaHCO_3$ and brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was

purified by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20) to afford 432 mg (83%) of glycolate **3i** as a yellow oil; IR: ν 2234, 1756, 1612, 1513, 1248, 1179, 1117, 1033, 820, 785, 700, 627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 3.0, 1.2 Hz, 1H), 7.33–7.27 (m, 4H), 7.26 (dd, J = 5.0, 3.0 Hz, 1H), 7.23–7.18 (m, 3H), 7.12 (dd, J = 5.0, 1.2 Hz, 1H), 6.88 (app d, J = 8.7 Hz, 2H), 5.68 (t, J = 6.6 Hz, 1H), 4.59 (s, 2H), 4.12 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.06 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 2.83 (t, J = 7.9 Hz, 2H), 2.27–2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 159.7 (C), 140.7 (C), 130.1 (CH), 130.0 (2CH), 129.9 (CH), 129.2 (C), 128.7 (2CH), 128.5 (2CH), 126.3 (CH), 125.5 (CH), 121.2 (C), 114.0 (2CH), 85.5 (C), 81.5 (C), 73.1 (CH_2), 66.9 (CH_2), 64.7 (CH), 55.4 (CH_3), 36.4 (CH_2), 31.5 (CH_2); HRMS (ESI) *m/z* calcd for $C_{25}H_{24}O_4SNa$ $[M + Na]^+$: 443.1287, found: 443.1289.

*1-Phenylbut-2-yn-1-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3j**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **3j** was isolated as a colorless oil (292 mg, 90%); IR: ν 1755, 1613, 1514, 1249, 1185, 1120, 1034, 821, 759, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 2H), 7.40–7.31 (m, 3H), 7.26 (app d, J = 8.7 Hz, 2H), 6.86 (app d, J = 8.7 Hz, 2H), 6.52 (q, J = 2.2 Hz, 1H), 4.55 (s, 2H), 4.12 (d_{ABsyst}, J = 16.6 Hz, 1H), 4.05 (d_{ABsyst}, J = 16.6 Hz, 1H), 3.79 (s, 3H), 1.90 (d, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 159.6 (C), 137.2 (C), 130.0 (2CH), 129.2 (C), 129.0 (CH), 128.7 (2CH), 127.8 (2CH), 113.9 (2CH), 84.5 (C), 75.6 (C), 73.0 (CH_2), 66.9 (CH_2), 66.6 (CH), 55.4 (CH_3), 3.9 (CH_3); HRMS (ESI) *m/z* calcd for $C_{20}H_{20}O_4Na$ $[M + Na]^+$: 347.1254, found: 347.1255.

*1-Phenylhex-4-yn-3-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3k**).*After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **3k** was isolated as a colorless oil (484 mg, 98%); IR: ν 2247, 1757, 1613, 1514, 1249, 1192, 1192, 1121, 1034, 821, 752,

701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33–7.26 (m, 4H), 7.22–7.16 (m, 3H), 6.89 (app d, J = 8.7 Hz, 2H), 5.44 (tq, J = 6.5, 2.1 Hz, 1H), 4.57 (s, 2H), 4.09 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.03 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.81 (s, 3H), 2.76 (t, J = 7.9 Hz, 2H), 2.15–2.03 (m, 2H), 1.87 (d, J = 2.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 159.6 (C), 140.9 (C), 130.0 (2CH), 129.3 (C), 128.6 (2CH), 128.5 (2CH), 126.2 (CH), 114.0 (2CH), 82.9 (C), 76.2 (C), 73.1 (CH_2), 66.9 (CH_2), 64.8 (CH_2), 55.4 (CH_3), 36.6 (CH_2), 31.4 (CH_2), 3.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_4Na$ $[M + Na]^+$: 375.1567, found: 375.1567.

*6-[(tert-Butyldiphenylsilyl)oxy]-1-phenylhex-4-yn-3-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3l**).* After purification by flash chromatography (petroleum ether/EtOAc = 90:10 to 80:20), **3l** was isolated as a colorless oil (412 mg, 93%); IR: ν 1759, 1613, 1514, 1249, 1176, 1111, 1086, 1035, 823, 741, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74–7.69 (m, 4H), 7.45–7.35 (m, 6H), 7.33–7.26 (m, 4H), 7.23–7.14 (m, 3H), 6.89 (d, J = 8.6 Hz, 2H), 5.46 (m, 1H), 4.57 (s, 2H), 4.38 (app br s, 2H), 4.07 (d_{ABsyst}, J = 16.5 Hz, 1H), 4.02 (d_{ABsyst}, J = 16.5 Hz, 1H), 3.80 (s, 3H), 2.72 (t, J = 7.9 Hz, 2H), 2.12–1.97 (m, 2H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5 (C), 159.6 (C), 140.7 (C), 135.7 (4CH), 133.13 (C), 133.11 (C), 129.97 (2CH), 129.95 (2CH), 129.2 (C), 128.5 (2CH), 128.5 (2CH), 127.9 (4CH), 126.3 (CH), 114.0 (2CH), 84.9 (C), 81.9 (C), 73.1 (CH_2), 66.8 (CH_2), 64.2 (CH), 55.4 (CH_3), 52.8 (CH_2), 36.2 (CH_2), 31.3 (CH_2), 26.8 ($3CH_3$), 19.3 (C); HRMS (ESI) *m/z* calcd for $C_{38}H_{42}O_5SiNa$ $[M + Na]^+$: 629.2694, found: 629.2689.

*1-(Benzyloxy)pent-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy]acetate (**3m**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **3m** was isolated as a colorless oil (479 mg, 99%); IR: ν 2246, 1758, 1613, 1513, 1247, 1189, 1109, 1031, 820, 739, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.25 (m, 7H), 6.87 (app d, J = 8.3 Hz,

2H), 5.68 (m, 1H), 4.60 (d_{ABsyst}, J = 12.1 Hz, 1H), 4.56 (s, 2H), 4.55 (d_{ABsyst}, J = 12.1 Hz, 1H), 4.13 (d_{ABsyst}, J = 16.6 Hz, 1H), 4.08 (d_{ABsyst}, J = 16.6 Hz, 1H), 3.79 (s, 3H), 3.71–3.63 (m, 2H), 1.83 (d, J = 2.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 159.6 (C), 137.7 (C), 130.0 (2CH), 129.3 (C), 128.6 (2CH), 127.9 (CH), 127.8 (2CH), 114.0 (2CH), 83.6 (C), 73.7 (C), 73.3 (CH_2), 73.0 (CH_2), 71.4 (CH_2), 66.8 (CH_2), 63.8 (CH), 55.4 (CH_3), 3.8 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{24}O_5Na$ $[M + Na]^+$: 391.1516, found: 391.1512.

*1-(Benzyloxy)-6-[(tert-butyldiphenylsilyl)oxy]hex-3-yn-2-yl 2-[(4-methoxyphenyl)methoxy] acetate (**3n**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **3n** was isolated as a pale yellow oil (540 mg, 97%); IR: ν 1758, 1612, 1513, 1248, 1175, 1108, 1084, 1033, 822, 739, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.63 (m, 4H), 7.44–7.34 (m, 6H), 7.32–7.23 (m, 7H), 6.85 (app d, J = 8.7 Hz, 2H), 5.71 (m, 1H), 4.57 (d_{ABsyst}, J = 12.1 Hz, 1H), 4.54 (s, 2H), 4.51 (d_{ABsyst}, J = 12.1 Hz, 1H), 4.08 (s, 2H), 3.79 (s, 3H), 3.74 (t, J = 7.0 Hz, 2H), 3.66 (dd, J = 11.0, 7.3 Hz, 1H), 3.62 (dd, J = 11.0, 4.2 Hz, 1H), 2.47 (td, J = 7.0, 2.0 Hz, 2H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (C), 159.6 (C), 137.7 (C), 135.7 (4CH), 133.6 (2C), 130.0 (2CH), 129.8 (2CH), 129.3 (C), 128.6 (2CH), 127.9 (CH), 127.84 (4CH), 127.82 (2CH), 114.0 (2CH), 85.0 (C), 75.6 (C), 73.2 (CH_2), 73.0 (CH_2), 71.5 (CH_2), 66.8 (CH_2), 63.6 (CH), 62.1 (CH_2), 55.4 (CH_3), 26.9 ($3CH_3$), 23.0 (CH_2), 19.3 (C); HRMS (ESI) *m/z* calcd for $C_{39}H_{44}O_6SiNa$ $[M + Na]^+$: 659.2799, found: 659.2802.

Difluorocyclopropenation of 3a: An oven-dried (resealable) vial was successively charged with NaF (1.7 mg, 0.040 mmol, 10 mol %), alkyne **3a** (166 mg, 0.400 mmol, 1 equiv) and diglyme (200 μL). The vial was closed with a Teflon coated rubber cap, flushed with argon and immersed in a pre-heated oil bath at 120 °C. To the resulting mixture (under argon atmosphere) was slowly added TFDA (300 μL, 1.20 mmol, 3.0 equiv) *via* syringe pump over

2 h. Once the addition was complete, the reaction mixture was stirred for further 15 min at 120 °C, cooled to rt and then directly subjected to purification by flash chromatography on silica gel (petroleum ether/Et_2O = 80:20) to afford 160 mg (86%) of **4a** as a colorless oil. This compound could be characterized but rapidly turned brown and underwent decomposition upon storage even in a freezer at –23 °C.

*1-(3,3-Difluoro-2-phenylcycloprop-1-en-1-yl)-3-phenylpropyl 2-[(4-methoxyphenyl)-methoxy]acetate (**4a**)*. IR: ν 1801, 1760, 1613, 1513, 1286, 1248, 1175, 1117, 1017, 823, 766, 692 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 7.67–7.62 (m, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.28–7.05 (m, 8H), 6.86 (d, J = 8.7 Hz, 2H), 5.98 (m, 1H), 4.54 (d_{ABsyst}, J = 11.4 Hz, 1H), 4.47 (d_{ABsyst}, J = 11.4 Hz, 1H), 3.99 (s, 2H), 3.39 (s, 3H), 2.78–2.64 (m, 2H), 2.21–2.05 (m, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 169.4 (C), 160.0 (C), 140.6 (C), 131.4 (CH), 130.9 (CH), 129.9 (2CH), 129.7 (C), 129.3 (2CH), 128.9 (2CH), 128.7 (2CH), 126.6 (2CH), 125.2 (C, t, $^2J_{C\text{-}F}$ = 11.6 Hz), 123.5 (C), 114.2 (2CH), 102.7 (C, t, $^1J_{C\text{-}F}$ = 272.4 Hz), 73.1 (CH_2), 68.4 (CH), 66.9 (CH_2), 54.8 (CH_3), 34.7 (CH_2), 31.3 (CH_2) *(The signal corresponding to one quaternary cyclopropene carbon was not visible presumably because of overlap with the solvent signal)*; ^{19}F NMR (282 MHz, C_6D_6) δ –106.1 (d_{ABsyst}, $^1J_{F\text{-}F}$ = 126.8 Hz, 1F), –107.4 (d_{ABsyst}, $^1J_{F\text{-}F}$ = 126.8 Hz, 1F); HRMS (ESI) *m/z* calcd for calcd for $C_{28}H_{26}F_2O_4Na$ $[M + Na]^+$: 487.1691, found: 487.1688.

Representative procedure for the difluorocyclopropenation/Ireland-Claisen rearrangement: An oven-dried (resealable) vial was successively charged with NaF (13.5 mg, 0.322 mmol, 10 mol %), alkyne **3a** (1.33 g, 3.22 mmol, 1.0 equiv) and diglyme (1.9 mL). The vial was closed with a Teflon coated rubber cap, flushed with argon and immersed in a pre-heated oil bath at 120 °C. To the resulting mixture (under argon atmosphere) was slowly added TFDA

(1.90 mL, 9.65 mmol, 3.0 equiv) *via* syringe pump over 2 h. Once the addition was complete, the reaction mixture was stirred for further 15 min at 120 °C, cooled to rt and then diluted with THF (56 mL). The resulting solution was sparged with argon for 15 min and then cooled to –78 °C. TMSCl (1.64 mL, 12.9 mmol, 4 equiv) and KHMDS (25.7 mL, 0.5 M solution in toluene, 12.9 mmol, 4 equiv) were successively added dropwise. After 1 h at –78 °C, the reaction mixture was warmed to rt, stirred for further 3 h and then poured into a saturated aqueous solution of NH_4Cl (100 mL). The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in a MeOH/toluene mixture (1:1, 20 mL) and trimethylsilyldiazomethane (3.2 mL, 2 M solution in Et_2O, 6.4 mmol, 2 equiv) was slowly added to the resulting solution. The reaction mixture was concentrated under reduced pressure and subsequent analysis of the residue by ^{1}H NMR spectroscopy indicated the formation of **8a** as a single detectable diastereomer (dr > 96:4). The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 90:10 to 80:20) to afford 1.10 g (72%) of **8a** as a pale yellow oil. On smaller scale, **8a** was obtained in similar yield (134 mg, 73%).

Methyl (2S)-2-[(1R*,3Z)-2,2-difluoro-1-phenyl-3-(3-phenylpropylidene)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8a**)*. IR: ν 1757, 1735, 1613, 1514, 1389, 1249, 1145, 1127, 1032, 1008, 823, 750, 721, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.23 (m, 9H), 7.23–7.15 (m, 3H), 6.90 (m, 2H), 6.64 (m, 1H), 4.72 (d_{ABsyst}, J = 11.4 Hz, 1H), 4.59 (d_{ABsyst}, J = 11.4 Hz, 1H), 4.05 (d, J = 2.2 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.92–2.82 (m, 2H), 2.69–2.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4 (C, d, $^4J_{C-F}$ = 1.9 Hz), 159.5 (C), 141.0 (C), 132.7 (CH), 131.4 (C, d, $^3J_{C-F}$ = 3.6 Hz), 130.5 (2CH), 129.8 (2CH), 129.5 (C), 128.58 (2CH), 128.56 (2CH), 128.3 (CH), 128.2 (2CH), 126.3 (CH), 122.9 (C, t, $^2J_{C-F}$ = 6.4 Hz),

113.9 (2CH), 107.6 (C, t, $^{1}J_{C-F}$ = 295.3 Hz), 78.4 (CH, d, $^{3}J_{C-F}$ = 3.9 Hz), 72.4 (CH_2), 55.4 (CH_3), 52.1 (CH_3), 41.7 (C, t, $^{2}J_{C-F}$ = 12.5 Hz), 34.4 (CH_2), 34.1 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –128.90 (d_{ABsyst}, $^{1}J_{F-F}$ = 168.2 Hz, 1F), –130.65 (d_{ABsyst}, $^{1}J_{F-F}$ = 168.2 Hz, 1F); HRMS (ESI) *m/z* calcd for $C_{29}H_{28}F_2O_4Na$ $[M + Na]^+$: 501.1848, found: 501.1842.

Methyl (2S)-2-[(1R*,3Z)-3-ethylidene-2,2-difluoro-1-(4-methoxyphenyl)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8b**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **8b** was isolated as a pale yellow oil (165 mg, 76%); IR: ν 1755, 1611, 1511, 1246, 1176, 1139, 1112, 1031, 1006, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (app d, *J* = 8.7 Hz, 2H), 7.18 (app d, *J* = 8.9 Hz, 2H), 6.81 (app d, *J* = 8.8 Hz, 2H), 6.73 (app d, *J* = 8.9 Hz, 2H), 6.46 (m 1H), 4.65 (d_{ABsyst}, *J* = 11.4 Hz, 1H), 4.51 (d_{ABsyst}, *J* = 11.4 Hz, 1H), 3.99 (d, *J* = 2.3 Hz, 1H), 3.73 (s, 3H), 3.68 (s, 3H), 3.56 (s, 3H), 1.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C, d, $^{4}J_{C-F}$ = 1.9 Hz), 159.6 (C), 159.5 (C), 131.6 (2CH, $^{5}J_{C-F}$ = 1.7 Hz), 129.8 (2CH), 129.5 (C), 128.2 (CH), 123.6 (C, t, $^{2}J_{C-F}$ = 5.7 Hz), 123.4 (C, d, $^{3}J_{C-F}$ = 3.7 Hz), 113.8 (2CH), 113.7 (2CH), 107.8 (C, t, $^{1}J_{C-F}$ = 294.9 Hz), 78.4 (CH, d, $^{3}J_{C-F}$ = 3.1 Hz), 72.3 (CH_2), 55.4 (CH_3), 55.3 (CH_3), 52.1 (CH_3), 41.5 (C, t, $^{2}J_{C-F}$ = 12.5 Hz), 18.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –131.2 (d_{ABsyst}, $^{1}J_{F-F}$ = 168.0 Hz, 1F), –133.2 (d_{ABsyst}, $^{1}J_{F-F}$ = 168.0 Hz, 1F); HRMS (ESI) *m/z* calcd for $C_{23}H_{24}F_2O_5Na$ $[M + Na]^+$: 441.1484, found: 441.1481.

*Methyl (2S)-2-[(1R,3Z)-3-ethylidene-2,2-difluoro-1-(4-methoxyphenyl)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate ((+)-**8b**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), (+)-**8b** was isolated as pale yellow oil (163 mg, 72%); $[\alpha]_D^{20}$ +61.8 (*c* 0.68, $CHCl_3$). The enantiomeric excess of (+)-**8b** (ee = 95%) was

determined by supercritical fluid chromatography analysis of compound (+)-**9b** obtained after cleavage of the PMB ether (*vide infra*).

Methyl (2S)-2-[(1R*,3Z)-1-(4-bromophenyl)-3-ethylidene-2,2-difluorocyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8c**).* After purification by flash chromatography (petroleum ether/EtOAc = 95:5 to 90:10), **8c** was isolated as a pale yellow oil (222 mg, 75%); IR: ν 1756, 1736, 1613, 1514, 1247, 1147, 1112, 1010, 824, 808, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (app d, J = 8.6 Hz, 2H), 7.31 (app d, J = 8.7 Hz, 2H), 7.22 (app d, J = 8.6 Hz, 2H), 6.88 (app d, J = 8.7 Hz, 2H), 6.56 (m, 1H), 4.72 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.57 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.07 (d, J = 2.2 Hz, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 2.01 (app br d, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (C, d, $^4J_{C-F}$ = 1.9 Hz), 159.5 (C), 132.22 (CH), 132.21 (CH), 131.3 (2CH), 130.6 (C, d, $^3J_{C-F}$ = 3.7 Hz), 129.8 (2CH), 129.21 (C), 129.15 (CH), 122.8 (C, t, $^2J_{C-F}$ = 6.0 Hz), 122.7 (C), 113.8 (2CH), 107.3 (C, t, $^1J_{C-F}$ = 293.4 Hz), 78.1 (CH, d, $^3J_{C-F}$ = 3.7 Hz), 72.5 (CH_2), 55.3 (CH_3), 52.2 (CH_3), 41.5 (C, t, $^2J_{C-F}$ = 12.6 Hz), 18.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{22}H_{21}BrF_2O_4Na$ $[M(^{79}Br) + Na]^+$ and $[M(^{81}Br) + Na]^+$: 489.0483 and 491.0463, found: 489.0438 and 491.0458.

Methyl (2S)-2-[(1R*,3Z)-1-(4-acetylphenyl)-3-ethylidene-2,2-difluorocyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8e**).* After purification by flash chromatography (petroleum ether/Et_2O = 90:10), **8e** was isolated as a pale yellow oil (156 mg, 65%); IR: ν 1758, 1687, 1609, 1516, 1267, 1251, 1149, 1120, 1035, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (app br d, J = 8.6 Hz, 2H), 7.45 (app d, J = 8.6 Hz, 2H), 7.32 (app d, J = 8.8 Hz, 2H), 6.90 (app d, J = 8.8 Hz, 2H), 6.61 (m, 1H), 4.74 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.59 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.11 (d, J = 2.3 Hz, 1H), 3.81 (s, 3H), 3.63 (s, 3H), 2.56 (s, 3H), 2.04 (app d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9 (C), 170.2 (C, d, $^4J_{C-F}$ =

1.9 Hz), 159.6 (C), 136.9 (C, d, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 136.8 (C), 130.8 (2CH), 129.8 (2CH), 129.5 (CH), 129.2 (C), 128.1 (2CH), 122.6 (C, t, $^{2}J_{C\text{-}F}$ = 6.1 Hz), 113.9 (2CH), 107.3 (C, t, $^{1}J_{C\text{-}F}$ = 295.4 Hz), 78.2 (CH, d, $^{2}J_{C\text{-}F}$ = 3.3 Hz), 72.6 (CH_2), 55.4 (CH_3), 52.2 (CH_3), 41.9 (C, t, $^{2}J_{C\text{-}F}$ = 12.7 Hz), 26.7 (CH_3), 18.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –130.66 (d_{ABsyst}, $^{1}J_{F\text{–}F}$ = 168.8 Hz), –133.04 (d_{ABsyst}, $^{1}J_{F\text{-}F}$ = 168.8 Hz); HRMS (ESI) *m/z* calcd for $C_{24}H_{24}F_2O_5Na$ $[M + Na]^+$: 453.1484, found: 453.1487.

Methyl (2S)-2-[(1S*,3Z)-1-(2-chlorophenyl)-3-ethylidene-2,2-difluorocyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8f**).* After purification by flash chromatography (petroleum ether/Et_2O = 90:10), **8f** was isolated as a pale yellow oil (222 mg, 67%); IR: ν 1755, 1613, 1514, 1205, 1175, 1246, 1147, 1108, 1038, 1004, 824, 757, 739 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6, 375K) δ 7.41–7.25 (m, 4H), 7.20 (app d, *J* = 8.6 Hz, 2H), 6.88 (app d, *J* = 8.7 Hz, 2H), 6.75 (app qt, *J* = 6.9, 1.7 Hz, 1H), 4.52 (d_{ABsyst}, *J* = 11.6 Hz, 1H), 4.45 (d_{ABsyst}, *J* = 11.6 Hz, 1H), 4.17 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H), 2.00 (dt, *J* = 6.9, 2.1 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 375K) δ 168.5 (C, d, $^{4}J_{C\text{-}F}$ = 1.9 Hz), 158.7 (C), 134.5 (C), 130.4 (C), 129.10 (CH), 129.07 (2CH), 128.8 (C), 128.6 (2CH), 125.8 (CH), 120.3 (C), 113.3 (2CH), 99.0 (C, t, $^{1}J_{C\text{-}F}$ = 314.8 Hz), 77.2 (CH), 71.1 (CH_2), 54.7 (CH_3), 51.1 (CH_3), 40.7 (C), 17.2 (CH_3) (*One quaternary aromatic carbon signal is not detected presumably because of overlap)*; ^{19}F NMR (282 MHz, $CDCl_3$, 295 K) The presence of a 72:28 mixture of rotamers was observed, δ –135.61 (d_{ABsyst}, $^{1}J_{F\text{-}F}$ = 165.2 Hz, 0.72 x 1F), –132.38 (d_{ABsyst}, $^{1}J_{F\text{-}F}$ = 173.5 Hz, 0.28 x 1F), –128.89 (d_{ABsyst}, $^{1}J_{F\text{-}F}$ = 173.5 Hz, 0.28 x 1F), –127.76 (d_{ABsyst}, $^{1}J_{F\text{-}F}$ = 165.2 Hz, 0.72 x 1F); HRMS (ESI) *m/z* calcd for $C_{22}H_{21}ClF_2O_4Na$ $[M(^{35}Cl) + Na]^+$ and $[M(^{37}Cl) + Na]^+$: 445.0989 and 447.0959, found: 445.0989 and 447.0962.

Methyl (2S)-2-[(1R*,3Z)-3-ethylidene-2,2-difluoro-1-(naphthalen-1-yl)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8g**).* After purification by flash chromatography (petroleum ether/Et_2O = 90:10), **8g** was isolated as a yellow oil (137 mg, 63%); IR: ν 1756, 1733, 1613, 1514, 1248, 1144, 1032, 822, 800, 778 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 375K) δ 8.23 (m, app br s, 1H), 7.89–7.82 (m, 2H), 7.50–7.40 (m, 4H), 7.18 (app d, J = 8.1 Hz, 2H), 6.87 (app d, J = 8.5 Hz, 2H), 6.82 (qt, J = 6.9, 2.0 Hz, 1H), 4.53 (d_{ABsyst}, J = 11.5 Hz, 1H), 4.45 (d_{ABsyst}, J = 11.5 Hz, 1H), 4.34 (s, 1H), 3.77 (s, 3H), 3.63 (br s, 3H), 2.02 (dt, J = 6.9, 2.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 296K) *Signals with an asterisk can be assigned to a minor rotamer when distinction is possible* δ 170.9* (C, d, $^4J_{C\text{-}F}$ = 2.0 Hz), 170.4 (C, d, $^4J_{C\text{-}F}$ = 1.6 Hz), 159.5* (C), 159.4 (C), 134.1* (C), 134.0 (C), 133.6 (C), 132.7* (C), 132.1 (CH), 130.15* (CH), 130.1 (C, d, $^4J_{C\text{-}F}$ = 3.9 Hz), 129.9* (CH), 129.7 (2CH), 129.35 (CH), 129.20* (CH), 129.16* (C), 129.14 (C), 129.0* (CH), 128.4* (CH), 128.37 (CH), 127.9 (CH), 127.4 (CH), 125.9 (CH), 125.76* (CH), 125.72 (CH), 125.34* (CH), 125.3* (CH), 124.8 (CH), 123.9* (CH), 123.5 (C, t, $^2J_{C\text{-}F}$ = 6.0 Hz), 113.8* (CH), 113.7 (2CH), 108.0 (C, t, $^1J_{C\text{-}F}$ = 295.5 Hz), 79.9 (CH, d, $^2J_{C\text{-}F}$ = 4.2 Hz), 77.8* (C), 72.7 (CH_2), 72.2* (CH_2), 55.4 (CH_3), 52.2* (CH_3), 52.0 (CH_3), 40.7 (C, t, $^2J_{C\text{-}F}$ = 13.1 Hz), 18.6* (CH_3), 18.5 (CH_3); HRMS (ESI) *m/z* calcd for $C_{26}H_{24}F_2O_4Na$ $[M + Na]^+$: 461.1535, found: 461.1532.

tert-Butyl 3-((1R,3Z)-3-ethylidene-2,2-difluoro-1-{(1S*)-2-methoxy-1-[(4-methoxyphenyl)methoxy]-2-oxoethyl}cyclopropyl)-1H-indole-1-carboxylate (**8h**).* After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8h** was isolated as a pale yellow oil (152 mg, 70%); IR: ν 1736, 1613, 1515, 1451, 1372, 1247, 1155, 1108, 822, 763, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06 (br d, J = 7.0 Hz, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.55 (s, 1H), 7.31 (d, J = 8.7 Hz, 2H), 7.24 (m, 1H), 7.15 (m, 1H), 6.87 (app d, J = 8.7 Hz, 2H), 6.62 (m, 1H), 4.72 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.58 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.11 (d, J = 2.2 Hz,

1H), 3.79 (s, 3H), 3.61 (s, 3H), 2.02 (d, J = 6.9 Hz, 3H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 159.5 (C), 149.6 (C), 135.3 (C), 130.3 (C), 129.9 (2CH), 129.3 (C), 129.1 (CH), 127.4 (CH), 124.3 (CH), 122.7 (C, t, $^2J_{C\text{-}F}$ = 5.8 Hz), 122.5 (CH), 120.6 (CH), 115.3 (CH), 113.8 (2CH), 111.3 (C), 107.5 (C, t, $^1J_{C\text{-}F}$ = 295.0 Hz), 83.9 (C), 77.9 (CH), 72.4 (CH_2), 55.4 (CH_3), 52.3 (CH_3), 36.0 (C, t, $^2J_{C\text{-}F}$ = 12.6 Hz), 28.3 ($3CH_3$), 18.4 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –129.50 (d_{ABsyst}, $^1J_{F\text{-}F}$ = 167.1 Hz), –134.04 (d_{ABsyst}, $^1J_{F\text{-}F}$ = 167.1 Hz); HRMS (ESI) *m/z* calcd for $C_{29}H_{31}F_2NO_6Na$ $[M + Na]^+$: 550.2012, found: 550.2008.

Methyl (2S)-2-[(1S*,3Z)-2,2-difluoro-3-(3-phenylpropylidene)-1-(thiophen-3-yl)-cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate* ***(8i)***. After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8i** was isolated as a yellow oil (129 mg**,** 70%); IR: ν 1756, 1613, 1514, 1249, 1145, 1125, 1033, 1011, 827, 750, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (app d, J = 8.7 Hz, 2H), 7.33–7.28 (m, 2H), 7.25–7.18 (m, 5H), 7.07 (dd, J = 4.2, 2.1 Hz, 1H), 6.92 (app d, J = 8.7 Hz, 2H), 6.61 (m, 1H), 4.76 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.62 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.03 (s, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.90 (t, J = 7.8 Hz, 2H), 2.72–2.63 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C), 159.5 (C), 140.9 (C), 132.8 (CH), 131.8 (C), 129.8 (2CH), 129.4 (C), 129.0 (CH), 128.57 (2CH), 128.56 (2CH), 126.3 (CH), 125.6 (CH), 125.1 (CH), 123.0 (C, t, $^2J_{C\text{-}F}$ = 6.3 Hz, C_6), 113.9 (2CH), 107.1 (C, t, $^1J_{C\text{-}F}$ = 296.2 Hz), 78.1 (CH), 72.4 (CH_2), 55.4 (CH_3), 52.2 (CH_3), 38.3 (C, t, $^2J_{C\text{-}F}$ = 12.9 Hz), 34.2 (CH_2), 34.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{27}H_{26}F_2O_4SNa$ $[M + Na]^+$: 507.1412, found: 507.1405.

Methyl (2S)-2-[(1R*,3Z)-2,2-difluoro-1-methyl-3-(3-phenylpropylidene)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate* ***(8k)***. After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8k** was isolated as a slightly yellow oil (216 mg, 61%); IR: ν 1752, 1734, 1614, 1515, 1250, 1106, 1033, 822, 751, 729, 700 cm^{-1}; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.33–7.24 (m, 4H), 7.22–7.16 (m, 3H), 6.87 (app d, J = 8.7 Hz, 2H), 6.21 (m, 1H), 4.58 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.51 (d_{ABsyst}, J = 11.3 Hz, 1H), 3.81 (d, J = 1.9 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 2.85–2.79 (m, 2H), 2.59–2.52 (m, 2H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C, d, $^4J_{C\text{-}F}$ = 2.5 Hz), 159.5 (C), 141.0 (C), 130.9 (CH), 129.8 (2CH), 129.3 (C), 128.51 (2CH), 128.47 (2CH), 126.2 (CH), 124.1 (C, t, $^2J_{C\text{-}F}$ = 6.2 Hz), 113.8 (2CH), 108.4 (C, t, $^1J_{C\text{-}F}$ = 295.6 Hz), 76.5 (CH, d, $^3J_{C\text{-}F}$ = 2.8 Hz), 71.7 (CH_2), 55.3 (CH_3), 52.2 (CH_3), 34.12 (CH_2), 34.06 (CH_2), 33.0 (C, t, $^2J_{C\text{-}F}$ = 12.1 Hz), 11.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{24}H_{26}F_2O_4Na$ $[M + Na]^+$: 439.1691, found: 439.1689.

Methyl (2S)-2-[(1S*,3Z)-1-{[(tert-butyldiphenylsilyl)oxy]methyl}-2,2-difluoro-3-(3-phenylpropylidene)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate* ***(8l)***. After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8l** was isolated as a pale yellow oil (112 mg, 48%); IR: ν 1756, 1613, 1587, 1514, 1248, 1142, 1112, 1081, 1034, 824, 744, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68–7.60 (m, 4H), 7.42–7.23 (m, 10H), 7.21–7.16 (m, 3H), 6.86 (app d, J = 8.7 Hz, 2H), 6.46 (app br t, J = 6.1 Hz, 1H), 4.64 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.50 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.35 (dd, J = 10.9, 3.1 Hz, 1H), 3.90 (d, J = 1.2 Hz, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.56 (dd, J = 10.9, 1.8 Hz, 1H), 2.85–2.78 (m, 2H), 2.62–2.52 (m, 2H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 159.4 (C), 141.0 (C), 135.79 (2CH), 135.76 (2CH), 133.20 (C), 133.14 (C), 133.0 (CH), 129.79 (CH), 129.75 (CH), 129.68 (2CH), 129.54 (C), 128.53 (2CH), 128.49 (2CH), 127.75 (2CH), 127.73 (2CH), 126.2 (CH), 121.3 (C, t, $^2J_{C\text{-}F}$ = 6.2 Hz), 113.8 (2CH), 107.9 (C, t, $^1J_{C\text{-}F}$ = 293.5 Hz), 74.3 (CH), 71.7 (CH_2), 59.3 (CH_2), 55.3 (CH_3), 52.1 (CH_3), 39.4 (C, t, $^2J_{C\text{-}F}$ = 11.3 Hz), 34.4 (CH_2), 34.1 (CH_2), 26.9 ($3CH_3$), 19.3 (C); HRMS (ESI) *m/z* calcd for $C_{40}H_{44}F_2O_5SiNa$ $[M + Na]^+$: 693.2818, found: 693.2815.

Methyl (2S)-2-[(1R*,3Z)-3-[2-(benzyloxy)ethylidene]-2,2-difluoro-1-methylcyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8m**).* After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8m** was isolated as a pale yellow oil (80 mg, 40%); IR: ν 1752, 1613, 1515, 1250, 1210, 1171, 1139, 1117, 1032, 822, 738, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 7H), 6.87 (app br d, J = 8.7 Hz, 2H), 6.22 (m, 1H), 4.60 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.56 (s, 2H), 4.52 (d_{ABsyst}, J = 11.3 Hz, 1H), 4.22–4.19 (m, 2H), 3.86 (d, J = 1.9 Hz, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C, d, $^4J_{C\text{-}F}$ = 2.5 Hz), 159.5 (C), 138.0 (C), 129.8 (2CH), 129.3 (C), 128.5 (2CH), 127.8 (CH), 127.7 (2CH), 127.3 (CH), 125.6 (C, t, $^2J_{C\text{-}F}$ = 6.4 Hz), 113.9 (2CH), 107.8 (C, t, $^1J_{C\text{-}F}$ = 294.1 Hz), 76.3 (CH, d, $^3J_{C\text{-}F}$ = 3.4 Hz), 72.8 (CH_2), 71.9 (CH_2), 69.1 (CH_2), 55.3 (CH_3), 52.3 (CH_3), 32.9 (C, t, $^2J_{C\text{-}F}$ = 12.1 Hz), 11.3 (CH_3, t, $^3J_{C\text{-}F}$ = 2.6 Hz); HRMS (ESI) *m/z* calcd for $C_{24}H_{26}F_2O_5Na$ $[M + Na]^+$: 455.1640, found: 455.1638.

Methyl (2S)-2-[(1R*,3Z)-3-[2-(benzyloxy)ethylidene]-1-{2-[(tert-butyldiphenylsilyl)oxy]-ethyl}-2,2-difluorocyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**8n**).* After purification by flash chromatography (petroleum ether/Et_2O = 80:20), **8n** was isolated as a pale yellow oil (59 mg, 43%); IR: ν 1753, 1613, 1514, 1250, 1175, 1112, 1034, 823 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.59 (m, 4H), 7.42–7.27 (m, 11H), 7.23 (app d, J = 8.8 Hz, 2H), 6.83 (app d, J = 8.8 Hz, 2H), 6.15 (m, 1H), 4.55 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.53 (s, 2H), 4.44 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.18–4.13 (m, 2H), 3.81 (d, J = 1.8 Hz, 1H), 3.80 (s, 3H), 3.78–3.62 (m, 2H), 3.61 (s, 3H), 2.21–2.11 (m, 1H), 2.05–1.94 (m, 1H), 1.01 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (C), 159.4 (C), 138.0 (C), 135.7 (4CH), 133.95 (C), 133.92 (C), 129.69 (2CH), 129.65 (2CH), 129.4 (C), 128.54 (2CH), 128.48 (CH), 127.9 (CH), 127.76 (2CH), 127.74 (2CH), 127.73 (2CH), 123.9 (C), 113.8 (2CH), 107.7 (C, t, $^1J_{C\text{-}F}$ = 297.4 Hz), 76.4 (CH), 72.8 (CH_2), 72.0 (CH_2), 69.0 (CH_2), 61.5 (CH_2), 55.4 (CH_3), 52.2 (CH_3), 34.7 (C, t,

$^{2}J_{C\text{-}F}$ = 12.2 Hz), 29.5 (CH_2), 26.9 ($3CH_3$), 19.3 (C); HRMS (ESI) *m/z* calcd for $C_{41}H_{46}F_2O_6SiNa$ $[M + Na]^+$: 723.2924, found: 723.2920.

Methyl (2S)-2-[(1R*,3Z)-2,2-difluoro-1-phenyl-3-(3-phenylpropylidene)cyclopropyl]-2-hydroxyacetate (**9a**).* To a solution of **8a** (478 mg, 1.00 mmol) in a CH_2Cl_2/aqueous buffer (pH = 7.2) mixture (4:1, 20 mL) was added DDQ (908 mg, 4.00 mmol, 4 equiv). After 6 h of vigorous stirring at rt, the reaction mixture was diluted with EtOAc (10 mL) and stirred for a further 15 min. The layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were successively washed with a 25% aqueous solution of $Na_2S_2O_3$, brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 90:10 to 80:20) to afford 269 mg (75%) of **9a** as a colorless oil; IR: ν 3510, 1742, 1603, 1390, 1254, 1218, 1145, 1121, 1097, 749, 717, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 7H), 7.21–7.16 (m, 3H), 6.62 (tt, *J* = 6.1, 2.0 Hz, 1H), 4.30 (d, *J* = 6.2 Hz, 1H), 3.72 (s, 3H), 3.10 (d, *J* = 6.2 Hz, 1H, OH), 2.92–2.83 (m, 2H), 2.69–2.60 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7 (C, t, $^{4}J_{C\text{-}F}$ = 2.0 Hz), 140.9 (C), 132.5 (CH), 130.8 (C, t, $^{3}J_{C\text{-}F}$ = 3.7 Hz), 130.2 (2CH), 128.6 (CH), 128.5 (4CH), 128.4 (2CH), 126.3 (CH), 123.0 (C, t, $^{2}J_{C\text{-}F}$ = 6.5 Hz), 107.5 (C, t, $^{1}J_{C\text{-}F}$ = 295.0 Hz), 72.0 (CH, dd, $^{3}J_{C\text{-}F}$ = 4.4, 3.0 Hz), 52.9 (CH_3), 42.4 (C, t, $^{2}J_{C\text{-}F}$ = 12.5 Hz), 34.3 (CH_2), 34.1 (CH_2); HRMS (ESI) *m/z* calcd for $C_{21}H_{20}F_2O_3Na$ $[M + Na]^+$: 381.1273, found: 381.1279.

*Methyl (2S)-2-[(1R,3Z)-3-ethylidene-2,2-difluoro-1-(4-methoxyphenyl)cyclopropyl]-2-hydroxy-acetate ((+)-**9b**).* Cleavage of the PMB ether in compound (+)-**8b** was achieved as under the conditions described for the formation of **9a** from **8a**. After purification by flash chromatography (petroleum ether/Et_2O = 90:10 to 80:20), alcohol (+)-**9b** was isolated as a

colorless oil (14 mg, 70%); $[\alpha]_D^{20}$ +40.4 (*c* 0.6, $CHCl_3$); IR: ν 3500, 1741, 1610, 1511, 1248, 1143, 1111, 1027, 834, 818, 736, 706 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (app d, J = 8.8 Hz, 2H), 6.84 (app d, J = 8.8 Hz, 2H), 6.52 (qt, J = 6.9, 2.3 Hz, 1H), 4.32 (dd, J = 6.6, 2.2 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.05 (d, J = 6.6 Hz, 1H, OH), 2.03 (dt, J = 6.9, 1.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9 (C, d, $^4J_{C\text{-}F}$ = 2.1 Hz), 159.8 (C), 131.40 (CH), 131.38 (CH), 128.0 (CH), 123.8 (C, d, $^2J_{C\text{-}F}$ = 6.2 Hz), 122.7 (C, d, $^2J_{C\text{-}F}$ = 3.8 Hz), 113.9 (2CH), 107.8 (C, t, $^1J_{C\text{-}F}$ = 294.3 Hz), 72.1 (CH, dd, $^3J_{C\text{-}F}$ = 4.5, 3.1 Hz), 55.3 (CH_3), 53.0 (CH_3), 42.2 (C, t, $^2J_{C\text{-}F}$ = 12.5 Hz), 18.4 (CH_3); HRMS (ESI) *m/z* calcd for $C_{15}H_{16}F_2O_4Na$ $[M + Na]^+$: 321.0909, found: 321.0908. The enantiomeric excess of (+)-**9b** was determined by supercritical fluid chromatography using a chiral stationary phase (AD-H column, 100 bar, 3 mL/min, $scCO_2$/MeOH = 96:4): minor enantiomer: t_R = 3.6 min; major (*S*)-enantiomer: t_R = 4.1 min. ee = 95%.

Methyl (1R,2S*,4S*,5R*)-6,6-difluoro-5-iodo-1-phenyl-4-(2-phenylethyl)-3-oxabicyclo-[3.1.0]hexane-2-carboxylate (**10a**).* To a solution of **9a** (35.8 mg, 0.100 mmol) in a MeCN/H_2O mixture (2:1, 6 mL) was added NIS (45.0 mg, 0.200 mmol). After 1 h stirring at 50 °C, the reaction mixture was diluted with EtOAc and H_2O. The layers were separated and the aqueous phase was extracted with EtOAc. The combined extracts were successively washed with a 15% aqueous solution of $Na_2S_2O_3$, a 1 M aqueous solution of NaOH, brine, then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/Et_2O = 90:10) to afford 48.3 mg (99%) of **10a** as a pale yellow oil; IR: ν 1749, 1603, 1297, 1219, 1162, 1105, 1076, 969, 758, 698, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.21 (m, 10H), 4.84 (d, J = 7.1 Hz, 1H), 4.67 (m, 1H), 3.75 (s, 3H), 3.04 (ddd, J = 14.0, 10.0, 3.9 Hz, 1H), 2.82 (ddd, J = 14.0, 9.5, 7.3 Hz, 1H), 2.39–2.31 (m, 1H), 2.22–2.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

167.5 (C), 141.1 (C), 130.9 (C, t, $^{4}J_{C\text{-}F}$ = 1.7 Hz), 130.2 (2CH), 128.9 (CH), 128.7 (2CH), 128.62 (2CH), 128.59 (2CH), 126.2 (CH), 110.6 (C, dd, $^{1}J_{C\text{-}F}$ = 314.7, 283.3 Hz), 88.4 (CH), 83.6 (CH), 52.7 (CH_3), 47.4 (C, dd, $^{2}J_{C\text{-}F}$ = 13.2, 9.2 Hz), 32.5 (CH_2), 32.4 (CH_2), 23.7 (C, t, $^{2}J_{C\text{-}F}$ = 11.3 Hz); HRMS (ESI) *m/z* calcd for $C_{21}H_{20}F_2IO_3$ $[M + H]^+$: 485.0420, found: 485.0421.

Methyl (2S)-2-[(1S*,3S*)-2,2-difluoro-1-phenyl-3-(3-phenylpropyl)cyclopropyl]-2-hydroxy-acetate (**11**).* To a solution of alkylidenecyclopropane **9a** (300 mg, 0.837 mmol) in CH_2Cl_2 (10 mL) was added Crabtree's catalyst [Ir]-**I** (40.5 mg, 50.3 μmol, 6 mol %) and the resulting mixture was stirred under an atmospheric pressure of hydrogen. After 18 h, the reaction mixture was concentrated under reduced pressure and analysis of the residue by ^{1}H NMR spectroscopy indicated the formation of a single detectable diastereomer. Purification by flash chromatography (petroleum ether/EtOAc = 80:20) afforded 275 mg (91%) of **11** as a colorless oil; IR: ν 3515, 1742, 1604, 1263, 1216, 1195, 1098, 748, 731, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.26 (m, 5H), 7.21–7.11 (m, 5H), 4.16 (br s, 1H), 3.81 (s, 3H), 2.74 (br s, 1H, OH), 2.68–2.53 (m, 2H), 2.10 (dddd, *J* = 14.8, 9.5, 5.1, 2.1 Hz, 1H), 1.83–1.73 (m, 2H), 1.67–1.56 (m, 1H), 1.16–1.05 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0 (C, d, $^{4}J_{C\text{-}F}$ = 2.6 Hz), 142.0 (C), 131.5 (2CH), 129.5 (C), 128.52 (2CH), 128.49 (2CH), 128.47 (CH), 128.41 (2CH), 126.0 (CH), 114.5 (C, dd, $^{1}J_{C\text{-}F}$ = 293.4, 288.7 Hz), 73.8 (CH, dd, $^{3}J_{C\text{-}F}$ = 7.8, 2.4 Hz), 52.8 (CH_3), 40.8 (C, dd, $^{2}J_{C\text{-}F}$ = 10.8, 8.8 Hz), 35.5 (CH_2), 31.2 (CH, t, $^{2}J_{C\text{-}F}$ = 9.6 Hz), 30.9 (CH_2), 24.1 (CH_2, d, $^{3}J_{C\text{-}F}$ = 2.7 Hz); HRMS (ESI) *m/z* calcd for $C_{21}H_{22}F_2O_3Na$ $[M + Na]^+$: 383.1429, found: 383.1430.

Methyl (2S)-2-[(1S*,3Z)-2,2-difluoro-1-(hydroxymethyl)-3-(3-phenylpropylidene)-cyclo-propyl]-2-[(4-methoxyphenyl)methoxy]acetate (**12**).* To a solution of **8l** (97.0 mg,

0.145 mmol) in THF (8 mL) at 0 °C, were subsequently added AcOH (41 μL, 0.72 mmol, 5 equiv) and *n*-Bu_4NF (0.72 mL, 1 M solution in THF, 0.72 mmol, 5 equiv). After 18 h at rt, the reaction mixture was hydrolyzed with a saturated aqueous solution of NH_4Cl. The resulting mixture was diluted with EtOAc, the layers were separated and the aqueous phase was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 80:20) to afford 34.1 mg (55%) of **12** as a colorless oil; IR: ν 3522, 1752, 1613, 1514, 1250, 1213, 1176, 1128, 1035, 823, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.25 (m, 4H), 7.22–7.16 (m, 3H), 6.88 (app d, J = 8.7 Hz, 2H), 6.26 (app tt, J = 6.1, 2.0 Hz, 1H), 4.63 (d_{ABsyst}, J = 11.2 Hz, 1H), 4.52 (d_{ABsyst}, J = 11.2 Hz, 1H), 3.93 (d, J = 1.5 Hz, 1H), 3.92–3.78 (br m, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 2.87–2.77 (m, 2H), 2.62–2.55 (m, 2H) (*OH not detected*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2 (C), 159.7 (C), 140.8 (C), 132.5 (CH), 130.0 (2CH), 128.7 (C), 128.6 (2CH), 128.5 (2CH), 126.3 (CH), 120.9 (C, t, $^3J_{C\text{-}F}$ = 6.6 Hz), 114.0 (2CH), 76.1 (CH, t, $^3J_{C\text{-}F}$ = 3.3 Hz), 72.4 (CH_2), 59.9 (CH_2), 55.4 (CH_3), 52.5 (CH_3), 38.5 (C, t, $^2J_{C\text{-}F}$ = 12.1 Hz), 34.3 (CH_2), 34.0 (CH_2) (*the signal corresponding to CF_2 is not seen unambigusouly because of its weak intensity*); HRMS (ESI) *m/z* calcd for $C_{24}H_{26}F_2O_5Na$ $[M + Na]^+$: 455.1640, found: 455.1639.

Methyl (2S)-2-[(1S*,3R*)-2,2-difluoro-1-(hydroxymethyl)-3-(3-phenylpropyl)cyclopropyl]-2-[(4-methoxyphenyl)methoxy]acetate (**13**).* Alkylidenecyclopropane **12** (35 mg, 0.081 mmol) was hydrogenated in the presence of Crabtree's Catalyst [Ir]-**I** (3.9 mg, 4.9 μmol, 6 mol %) in CH_2Cl_2 (2 mL). After 18 h at rt, the reaction mixture was concentrated under reduced pressure and analysis of the residue by ^1H NMR spectroscopy indicated the formation of a single detectable diastereomer (dr > 96:4). The crude material was purified by flash chromatography

on silica gel (petroleum ether/EtOAc = 80:20) to afford 32.3 mg (92%) of **13** as a colorless oil; IR: ν 3518, 1752, 1615, 1516, 1252, 1216, 1109, 1036, 825, 752, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ ^1H NMR (400 MHz, $CDCl_3$) δ 7.31–7.26 (m, 4H), 7.22–7.15 (m, 3H), 6.88 (app d, J = 8.7 Hz, 2H), 4.59 (d_{ABsyst}, J = 11.0 Hz, 1H), 4.47 (d_{ABsyst}, J = 11.0 Hz, 1H), 3.98 (d, J = 1.5 Hz, 1H), 3.91 (ddd, J = 12.4, 7.0, 3.0 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.70–3.64 (m, 1H), 2.72–2.56 (m, 2H+OH), 1.79–1.66 (m, 3H), 1.66–1.56 (m, 1H), 1.46–1.36 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7 (C, d, $^4J_{C\text{-}F}$ = 2.9 Hz), 159.7 (C), 141.9 (C), 129.9 (2CH), 128.9 (C), 128.51 (2CH), 128.46 (2CH), 126.0 (CH), 114.0 (2CH), 74.8 (CH, dd, $^3J_{C\text{-}F}$ = 7.1, 1.6 Hz), 72.6 (CH_2), 61.0 (CH_2, d, $^3J_{C\text{-}F}$ = 6.0 Hz), 55.4 (CH_3), 52.6 (CH_3), 36.0 (C, t, $^2J_{C\text{-}F}$ = 11.0, 7.9 Hz), 35.4 (CH_2), 31.1 (CH_2), 30.4 (CH, t, $^2J_{C\text{-}F}$ = 10.1 Hz), 22.8 (CH_2) (*the signal corresponding to CF_2 is not seen unambigusouly because of its weak intensity*); HRMS (ESI) *m/z* calcd for $C_{24}H_{28}F_2O_5Na$ $[M + Na]^+$: 457.1797, found: 457.1794.

(1S,3S*)-2,2-Difluoro-1-phenyl-3-(3-phenylpropyl)cyclopropane-1-carboxaldehyde (**14**).* To a solution of α-hydroxy ester **13** (10 mg, 0.028 mmol) in THF (2 mL) at 0 °C, was added $LiAlH_4$ (2.1 mg, 0.055 mmol). After 1 h at rt, the reaction mixture was diluted with CH_2Cl_2 and poured into a 10% aqueous solution of Rochelle's salt. After 1 h stirring, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL) and $NaIO_4$ adsorbed on silica gel (80 mg, 14.9% w/w, 0.056 mmol) was added. After 1 h stirring at rt, the reaction mixture was filtered through a short plug of Celite (CH_2Cl_2), the filtrate was evaporated under reduced pressure and the residue was purified by chromatography on a preparative silica gel plate (petroleum ether/Et_2O = 90:10) to afford 6.0 mg (72%) of **14** as a colorless oil; IR: ν 1719, 1604, 1454, 1261, 1195, 1151, 1113, 1018, 750, 724, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) ^1H NMR

(400 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.44–7.39 (m, 3H), 7.31–7.16 (m, 5H), 7.16–7.12 (m, 2H), 2.75 (dddd, J = 14.9, 9.5, 5.2, 3.6 Hz, 1H), 2.69–2.52 (m, 2H), 1.86–1.74 (m, 2H), 1.64–1.54 (m, 1H), 1.25–1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.0 (CH, dd, $^4J_{C-F}$ = 4.4, 3.1 Hz), 141.6 (C), 131.3 (2CH), 129.1 (2CH), 128.94 (C), 128.86 (CH), 128.6 (2CH), 128.4 (2CH), 126.1 (CH), 114.0 (C, dd, $^1J_{C-F}$ = 294.8, 291.2 Hz), 49.6 (C, dd, $^2J_{C-F}$ = 12.6, 8.7 Hz), 35.4 (CH_2), 33.4 (CH, t, $^2J_{C-F}$ = 9.3 Hz), 30.4 (CH_2), 23.4 (CH_2, d, $^3J_{C-F}$ = 2.7 Hz); HRMS (ESI) *m/z* calcd for $C_{19}H_{19}F_2O$ $[M + H]^+$: 301.1398. Found: 301.1410.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds, ^{19}F NMR spectra of selected representative compounds, data relative to the determination of the optical purities of (*S*)-**1b** and (+)-**8b** by supercritical fluid chromatography (SFC).

ACKNOWLEDGEMENT

One of us (G.E.) thanks Diverchim for a CIFRE grant.

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